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Prospective audit of adverse reactions occurring in 459 primary antibody-deficient patients receiving intravenous immunoglobulin

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SUMMARY

Intravenous immunoglobulin (IVIG) is used as the standard replacement therapy for patients with primary antibody deficiencies. A previous study of adverse reactions in patients self-infusing at home over 1 year showed an overall reaction rate of 0·7%. A larger prospective study is reported here, involving a greater number of immunology centres and including children and adults who received infusions from medical or nursing staff as well as those self-infusing. Four hundred and fifty-nine patients were entered into this study and 13 508 infusions were given. The study showed that no severe reactions occurred and the reaction rate was low at 0·8%. This figure could have been lower, 0·5%, if predisposing factors responsible for some reactions had been considered before infusion. In conclusion, the study shows the importance of ongoing training for patients and staff to recognize the predisposing factors to prevent avoidable reactions. Because none of these reactions were graded as severe, the present guidance to prescribe self-injectable adrenaline for patients infusing outside hospital should be reviewed.

Keywords adrenaline adverse reactions intravenous immunoglobulin primary antibody deficiency

INTRODUCTION

An adverse reaction study for patients with primary antibody deficiency self-infusing intravenous immunoglobulin (IVIG) at home was conducted over 1 year in 1993–94. This first prospective study involved 119 adult patients from four centres: Oxford, Birmingham, Nottingham and Manchester. The aim of the study was to record the incidence of all adverse reactions and possible reasons for the reactions. The study showed that the overall reaction rate in patients who self-infused replacement doses of IVIG at home was low (0·7%) [1]. At the end of the 12-month period it was agreed to conduct a larger study to include more immunology centres and to enter both adults and children infusing either at home or under medical or nursing supervision.

We now report the results of a prospective study of 459 patients receiving such immunoglobulin therapy who were studied for a further 2 years.

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MATERIALS AND METHODS

Study design

This was a multi-centre study and data was collected from 12 centres: The Hospital for Sick Children, Great Ormond Street; St Helier Hospital, Carshalton; South-western Blood Transfusion Service, Bristol; Royal Victoria Hospital, Belfast; Newcastle General Hospital; Royal Brompton Hospital, London; Royal Free Hospital, London; Oxford Radcliffe Hospital; Birmingham Heartlands Hospital; Queens Medical Centre, Nottingham; Salford Royal Trust, Manchester and St James Hospital, Leeds. Two centres collated the study data, Birmingham and Oxford; the final analysis was conducted in Oxford. Six different immunoglobulin products were used throughout the study.

Patients with primary antibody deficiencies, who were established on stable IVIG treatment having received at least six infusions, were included in the study. Patients were not selected – the centres who agreed to take part entered all patients receiving treatment at that centre, provided they had received at least six infusions uneventfully. These patients received doses of 300–

600 mg/kg/month [2] and the IVIG was given at the rate recommended by the specific manufacturer. The decisions regarding the place of infusion are determined by the criteria in the UK Home Immunologlobulin Therapy Guidelines, approved by the Department of Health in 1990 and updated in 1999. The place of infusion was unchanged during the study period, enabling the patients to be asigned to one of the following groups:

- Established: those self-infusing IVIG and established on home therapy (EST);
- GP-based: those self-infusing IVIG at their GP's surgery on a shared care basis (GP); and
- Out-patient based: those receiving regular infusions in hospital as an out-patient (OP).

Data collection

Data were collected prospectively. The immunology nurse from each centre completed an entry form for each patient in the study recording demographic information and occupational status. Data were collected on all forms and consent was not obtained, although patients were informed that this study was ongoing. If there was any change in subject details, for example change of immunoglobulin product, patient type or if the patient was withdrawn from immunoglobulin therapy for any reason, an update form was completed and sent to the data collection centre.

Patients self-infusing IVIG completed an infusion record documenting details of each infusion, including batch numbers of the immunoglobulin product. In the event of an adverse reaction the details were reported on a 'patient adverse reaction form' specifying symptoms, duration of event and action taken. This form, together with the infusion record, was sent to the immunology nurse for review, and from this information the 'study adverse reaction form' was completed. Predisposing factors for the reaction such as the presence of infection were detailed, whether the reaction occurred despite prior prophylaxis, what action had been taken and the subsequent management after the reaction, were recorded. The severity of the adverse event was defined according to the classification of mild, moderate or severe [3]. An adverse reaction occurring in the hospital out-patient clinic or in the GP surgery was recorded by the health professional on the study adverse reaction form.

Each centre completed a quarterly report recording patient name and type, immunoglobulin product, total number of infusions and how many of the infusions were given with or without prophylaxis or with an infection present. All adverse reactions were documented regardless of severity. Centres vary in policy relating to selection of prophylaxis.

Classification of reactions

Reactions occurred during or within 48 h of the infusion and were classified as mild, moderate or severe and were defined as follows:

- *Mild reactions*: symptoms included headache, flushing, muscle aches, shivering, feeling sick, itching, urticaria, anxiety, lightheadedness, dizziness or irritability. These subsided when the infusion rate was decreased.
- *Moderate reactions* included mild reactions becoming worse, or other symptoms such as chest pain or wheezing, necessitating the infusion to be discontinued.
- *Severe reactions* included moderate reactions persisting or becoming worse, or other symptoms such as tightness of the throat, severe headache and shaking, severe breathlessness or wheezing, severe dizziness or fainting, sensation of pressure in the chest or collapse. A severe reaction would have required the administration of adrenaline and medical attention.

All EST patients carried self-injectable adrenaline for use in the event of a serious adverse reaction; they have been instructed on the recognition and treatment of reactions and their competence documented before infusing at home [4].

The severity grading of all reactions was confirmed by independent review.

Method of administration of IVIG

The infusions were administered using a 23-g butterfly type needle and an administration set with a 15-μ filter. The rate of the infusion was calculated from the patient's body weight; 4 ml/min was the maximum rate advised. Infusion pumps were not usually necessary as drip rates were easily monitored. Blood samples were taken at regular intervals (usually 6–8 weekly) for liver function tests, C-reactive protein and preinfusion (trough) IgG levels.

Prophylaxis for infusions

Prophylaxis is used regularly in new patients for the first two infusions but rarely in established patients, unless they have had a previous reaction or are at increased risk of reaction, such as during an intercurrent infection. Prophylaxis involves the use of one or several agents including: hydrocortisone i.v. (100 mg for adults, given immediately prior to the infusion), oral antihistamines, paracetamol or aspirin given up to 1 h prior to the infusion. The use of prophylaxis is variable between centres and was at the discretion of the centre.

RESULTS

A total of 459 patients were entered into the study over 2 years, 261 male and 198 female. The age range was from 2 to 88 years, 92 being under 18 years of age. Two hundred and ninety patients were self-infusing at home (72 were under 18 years); 160 were infused as out-patients (19 were under 18 years); nine infused in their GP's surgery (one was under 18 years).

Over the 2 years of the study, a total of 13 508 infusions were recorded. Seven hundred and twenty-seven infusions were given with routine prophylaxis in the absence of infection. One thousand and one infusions were given with a mild infection present, of which 192 received prophylaxis.

Thirty patients were withdrawn from the study for the following reasons

Fifteen died (deaths unrelated to IVIG treatment), four changed to subcutaneous immunoglobulin treatment, one patient was withdrawn from therapy following 11 adverse reactions, nine were withdrawn for various clinical reasons such as moving away, or discontinuation of therapy and one at the patient's own request. All were included in the analysis up to withdrawal.

There were 111 documented adverse reactions in 13 508 infusions, of which 91 were mild and 20 were moderate. No severe reactions occurred. There were 87 reactions in EST patients and 24 reactions in GP or out-patients (see Table 1). The overall reaction rate was 0·8%.

The patients were grouped by location of infusions and by age (Table 1). The reaction rate in adults was 0·8%, in young adults

(10–17 years) the rate was 0·8% and in children under the age of 10 years it was 0·7%.

Severity of reactions

Mild. The 91 reactions classified as mild consisted of headache, chills, nausea, itching (see Fig. 1); none of these reactions required the infusion to be stopped. Forty-four patients had mild reactions; one patient reported 19 reactions. From these 91 mild reactions, 74 occurred in 35 adults, 17 occurred in nine children under 18 years.

Moderate. The 20 reactions defined as moderate occurred in 15 patients (see Table 2). One patient reported four reactions. Two moderate reactions occurred in two children. Following a moderate reaction the subsequent infusion was administered under medical or nursing supervision. This happened in nine cases. In five of the cases, the patients continued with the infusion; advice only was given in two cases and one patient was withdrawn from treatment after four reactions. A further two patients required a change of immunoglobulin product (Table 2).

Reactions per patient

Four hundred patients did not have any reaction to immunoglobulin infusions; 59 patients had either mild or moderate reactions. These tended to occur in those patients who had experienced adverse events previously. One child (under 9 years old) had five reactions. In the other children experiencing reactions, one had two reactions, one had three reactions, one had four reactions and the rest (five) had only one reaction. Of the adult patients, 16 experienced two or more (but less than five) reactions and one patient reported 19 reactions.

Timing of reactions

Of the 111 reactions, only 12 occurred within 30 min of the start of the infusion and only one within 10 min. Of these, none required the infusion to be stopped, no treatment was given and there were no sequelae.

Associated factors (Table 3)

Infection. There were 111 adverse reactions of which 23 were reported as associated with an intercurrent infection. A further 28 reactions occurred when an infusion was received at a time of infection, implying that this may have been a contributory factor. In one patient with an intercurrent infection a reaction occurred despite prophylaxis with hydrocortisone and an oral antihistamine.

There were 1001 infusions performed at a time of infection; the overall rate of reactions occurring when an infusion was given during an infection was 51/1001 (5·1%). This compares with

Table 1. Infusions and reactions by age of patient and locality of infusion

	All reactions											
Site of infusions	EST			OP			GP			Total		
Age (years)	No. of ADR	No. Inf.	%	No. of ADR	No. Inf.	%	No. of ADR	No. Inf.	%	Total no. ADR	No. Inf.	Total
0–9	7	837	0·84	0	212	0	0	0	0	7	1 049	0·67
10–17	12	1227	0·98	0	3195	0	0	33	0	12	1 455	0·82
18+	68	7410	0·92	16	3339	0·48	8	255	3·14	92	11 004	0·84
Total	87	9474	0·92	16	3746	0·43	8	288	2·78	111	13 508	0·82

EST: established home infusions, OP: out-patient, GP: general practitioner; ADR: adverse reactions; No. Inf.: number of infusions.

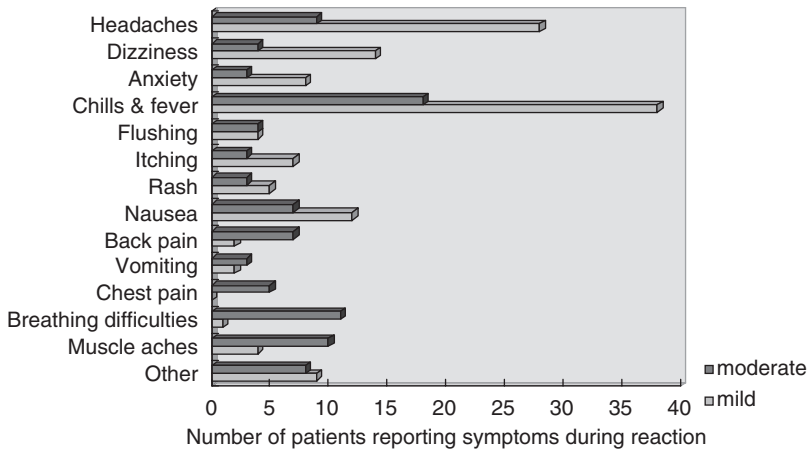

Fig. 1. Symptoms observed during mild and moderate reactions.

Table 2. Management of moderate reactions

Age	Patient type	No. of reactions	Predisposing factors	Subsequent management
<18	EST	1	Not known	Reviewed in hospital and brought in for next infusion
<18	EST	1	Nil	Brought in for next infusion
>18	OP	1	Nil	Change of product for next infusion in hospital
>18	EST	2	1. Concomitant infection	Advice given
			2. Not known	Brought in for next infusion
>18	EST	1	Concomitant infection	Continued as before
>18	EST	1	Not known	Brought in for next infusion
>18	EST	1	Not known	Continued as before
>18	EST	4	Not known × 4	Withdrawn from treatment after 4th reaction
>18	GP	2	1. Anti-IgA antibodies	1. Reviewed in hospital; brought in for next infusion
			2. Anti-IgA antibodies, titre 1/2048	2. Reviewed in hospital; brought in for next infusion; change of product
>18	EST	1	Concomitant infection; delay since last infusion; drop rate too fast	Advice given
>18	EST	1	Concomitant infection; delay since last infusion	Brought in for next infusion
>18	OP	1	Concomitant infection; delay since last infusion	Continued as before
>18	EST	1	Concomitant infection	Continued as before
>18	EST	1	Not known	Brought in for next infusion
>18	OP	1	Concomitant infection; delay since last infusion	Continued as before

$n = 20$. EST: established home infusions; OP: out-patient; GP: general practitioner.

Table 3. Reactions with associated factors

Factor	EST	GP and OP	Totals
Known infection	19	4	23
Delay since last infusion	10	3	13
Too fast	5	0	5
Anti-IgA antibodies	0	4	4
None	48	18	66
Total	82	29	111

Possible infection = 28. EST: established home infusions; OP: out-patient; GP: general practitioner.

Table 4. The incidence of reactions between centres

	Reactions	Infusions	% Rate
Centre A	14*	597	2·35
Centre B	11	1 077	1·02
Centre C	22	1 788	1·23
Other centres together	45	10 027	0·45

*19 reactions in one patient – patient excluded from this part of the study.

12 507 infusions while there was no infection, during which there were 60 reactions (0·48%).

Rate of infusion. In five reactions, the rate of infusion was documented as being faster than the rate recommended by the manufacturer.

Increase of interval since last infusion. In 13 reactions there had been a delay in administering the infusion. Because delay is often due to an untreated infection, such a reaction may also be due to intercurrent infection.

Anti-IgA antibodies. These were documented in only two patients and associated with reactions on only four occasions; however, as their presence or absence was not routinely tested, the relevance is unknown [5].

Prophylaxis. Of the 111 reactions, 47 occurred despite prophylaxis. Such prophylaxis included 10 episodes of antihistamine usage, 17 of antihistamine plus aspirin, two despite aspirin alone, 18 despite paracetamol and two despite antihistamine plus paracetamol.

Variation between centres. The incidence of reactions did vary between centres (see Table 4), with the highest rates in three centres being higher that the summed data from the other centres together.

Variation between IVIg products. There were no differences between preparations.

DISCUSSION

Patients with primary antibody deficiencies require lifelong treatment with immunoglobulin and many of these patients receive their treatment by self-administering immunoglobulin by the intravenous route at home. All patients are taught to recognize the symptoms of a reaction and to treat according to protocol. They are prescribed a fixed dose of adrenaline for treatment of any serious adverse reaction. The finding that no reaction was severe and the adrenaline was not used in 13 508 infusions in 459 patients questions the need for this practice to continue.

The safety of home infusions (EST) *versus* infusions in out-patient departments or in a GP's surgery was also considered. In this study, all the patients self-infusing at home had been trained in all aspects of intravenous infusion, and all had received formal training in prevention of adverse reactions [4]. However, 87 reac-

tions still occurred in the EST patients. Seventy-two were classified as mild and 15 were classified as moderate.

Twenty-four reactions occurred during infusions administered under medical (GP) or nursing (out-patient) supervision. The locality of infusion did not affect the adverse reaction rate, including the apparent higher rate of reactions in community surgeries, as the numbers of infusions is small. Adverse reaction rates were independent of age.

Preventable causes of reactions [3] were identified in 45 patients. On a further 66 occasions there were no obvious reasons for the reactions. (The patient who had a total of 19 mild reactions would have benefited from an earlier change of product.) Once preventable factors were taken into consideration, the figures showed that a total of 66 reactions occurred in 13 508 infusions, making the overall reaction rate of all infusions had been given strictly in accordance with protocol of 0·5%.

The differences in the incidences of reactions between centres is of interest and emphasizes the need for continual audit so that individual centres can compare their practice with that of their peers.

The study has shown that no serious reactions occurred in a total of 13 508 infusions. Data from previous studies have showed no serious reactions occurred in 2715 infusions [1,6]. Therefore in a total of 16 223 intravenous immunoglobulin infusions no serious adverse reactions have occurred; over 11 500 of these infusions were self-administered at home safely. Furthermore, only 12 reactions occurred within 30 min of the start of the infusion and none were thought to be anaphylactic in origin, as all were classified as mild, the infusions were continued uneventfully and none required treatment.

When prescribing adrenaline it is important to consider the possibility of drug interactions with beta-blockers or antidepressants which may interfere with adrenaline efficacy (beta-blockers) [7] or lead to potentially serious cardiovascular adverse effects (tricyclic antidepressants) [8]. There is also the serious risk of adrenaline being injected inadvertently into a digit. An incident of this has been reported outside the study when, in a stressful situation, an Epipen® was used mistakenly upside-down.

In the light of the above evidence, is it necessary to prescribe adrenaline for all patients at home self-administering intravenous immunoglobulin, or should this practice be abandoned in view of the risks of misusing or mishandling this potent drug? The cost of the patients at home having Epipens® is in the region of £20 000 per year. As the above evidence has shown, the risk of an adverse event requiring adrenaline is minimal; is this cost justifiable?

CONCLUSIONS

This study has shown that the incidence of adverse reactions in patients receiving intravenous immunoglobulin is very low when patients have been stabilized on treatment. It has shown the importance of medical and nursing staff or, in the case of home treatment, patients and partners, being fully trained in the risk associated with delaying infusions. Also be reminded of the risks of infusing at a time of intercurrent infection and of exceeding the recommended maximum administration rate. It is essential to be fully trained in the prevention, recognition and treatment of adverse reactions; furthermore, regular assessment and continual education of staff and patients who administer intravenous immunoglobulin infusions is necessary to prevent avoidable reactions. This had been incorporated into the accreditation standards for centres delivering care to patients with primary immune deficiencies (UKPIN).

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REFERENCES

1 Brennan VM, Cochrane S, Fletcher C, Hendy D, Powell P. Surveillance of adverse reactions in patients self-infusing intravenous immunoglobulin at home. J Clin Immunol 1995; **15**:116–9.

2 Chapel HM for the Consensus Panel. Consensus on diagnosis and management of primary antibody deficiencies. Br Med J 1994; **308**:581–5.

3 Misbah SA, Chapel HM. Adverse effects of intravenous immunoglobulin. Drug Safety 1993; **9**:254–62.

4 Chapel HM, Brennan VM, Delson E. Immunoglobulin replacement therapy by self-infusion at home. J Clin Immunol 1988; **73**:160–2.

5 Bjorkander J, Hammarstrom L, Smith CIE, Buckley R, Cunningham-Rundles C, Hanson LA. Successful immunoglobulin prophylaxis in patients with antibody deficiency syndromes in the presence of anti-IgA. J Clin Immunol 1987; **7**:8–15.

6 Chapel HM, Spickett GP, Ericson D, Engl W, Eibl MM, Bjorkander J. The comparison of the efficacy and safety of intravenous versus subcutaneous immunoglobulin replacement therapy. J Clin Immunol 2000; **20**:94–100.

7 Toogood JH. Risk of anaphylaxis in patients receiving beta-blocker drugs. J Allergy Clin Immunol 1988; **81**:1–5.

8 Goulet JP, Perusse R, Turcotte JY. Contraindications to vasoconstrictors in dentistry: Part III. Pharmacologic interactions. Oral Surg Oral Med Oral Path 1992; **74**:692–7.